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Size Dependence of the End-Systolic Stress/Volume Ratio in Humans: Implications for the Evaluation of Myocardial Contractile Performance In Pressure and Volume Overload

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The end-systolic stress/volume ratio is currently recognized as a relatively load-independent index of myocardial contractile performance, but its dependence on ventricular size may limit its value for interpatient comparisons. In this study, the relation between the end-systolic stress/volume ratio and left ventricular end-diastolic volume was angiographically analyzed in 104 patients with normal coronary angiograms. Eighteen patients had a normal ventricle, 24 had aortic stenosis, 18 had aortic regurgitation, 9 had mitral regurgitation and 35 had cardiomyopathy.

An inverse relation between the end-systolic stress/volume ratio and left ventricular end-diastolic volume was demonstrated in the normal group ($r = 0.72$, $p < 0.001$); subjects with a larger left ventricle had a reduced index but, presumably, the same degree of contractility as that of subjects with a smaller ventricle. Attempts to normalize values by using end-diastolic volume or body surface area were unsuccessful. A similar inverse relation was demonstrated in the aortic stenosis group ($r = 0.48$, $p < 0.05$), probably because hypertrophy helps to keep wall stress normal or low despite progressive ventricular enlargement in these patients. The end-systolic stress/volume ratio was also inversely related to left ventricular chamber size in patients with volume overload due to aortic regurgitation ($r = 0.80$, $p < 0.001$) and in those with cardiomyopathy ($r = 0.84$, $p < 0.001$). However, at a given left ventricular end-diastolic volume, the end-systolic stress/volume ratio was higher in patients with aortic regurgitation than in those with cardiomyopathy, suggesting better contractile performance for a comparable degree of ventricular dilation. Finally, patients with aortic stenosis and cardiomyopathy with comparable end-diastolic volumes had similar end-systolic ratios.

These data provide evidence that the end-systolic stress/volume ratio is highly dependent on the size of the left ventricular chamber in humans and that this dependence differs according to the nature of the underlying myocardial disease.

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Characterization of left ventricular contractile performance in patients with pressure or volume overload remains a difficult challenge. Isovolumetric or ejection phase (1,2) indexes depend heavily on the loading conditions of the heart. The slope of the pressure-volume relation at end-systole—called E_{max} by Suga and Sagawa (3)—has been considered for assessing contractile performance in view of its sensitivity to inotropic changes and relative independence from ventricular load. Because the determination of E_{max} requires obtaining pressure/volume curves at different loads, attempts have been made to individualize a simpler index in humans. The end-systolic wall stress/volume ratio is easily obtained during routine cardiac catheterization and has been established as a reasonably load-independent index of myocardial contractile performance (4–7). Like most indexes, however, this ratio does not take into account the diastolic dimensions of the left ventricle.

Suga et al. (8) reported the size dependence of E_{max} in experimental conditions, and it has since been emphasized that left ventricular function indexes in humans should be normalized (9–11) to enable comparisons of contractile function among patients, especially in those with a dilated or hypertrophied ventricle or both. An additional problem is that the size dependence of an elastance-derived index may differ according to the origin of the pathologic process: Is the dependence of the end-systolic stress/volume ratio on left ventricular size similar in normal subjects, in patients with pressure overload and in those with volume overload?

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The present study was designed 1) to relate the end-systolic stress/volume ratio to left ventricular end-diastolic volume in patients with a normal ventricle, and 2) to analyze the end-systolic stress/volume ratio–end-diastolic volume relation in patients with aortic stenosis, aortic regurgitation, mitral regurgitation and intrinsic alteration of contractile performance due to cardiomyopathy.

Methods

Study patients. Hemodynamic investigation was performed in a total of 104 patients. All had normal coronary arteriograms. Eighteen patients (6 men and 12 women with a mean age of 45 ± 12 years) had no significant valvular, hypertensive or congenital heart disease and formed the normal group. Twenty-four patients (11 men and 13 women with a mean age of 65 ± 11 years) had isolated aortic stenosis without significant regurgitation. Eighteen patients (13 men and 5 women with a mean age of 50 ± 15 years) had isolated aortic regurgitation. Nine patients (7 men and 2 women with a mean age of 58 ± 18 years) had isolated mitral regurgitation and formed the mitral regurgitation group. Thirty-five patients had cardiomyopathy without significant valvular disease. Informed consent was obtained from each patient before the study. Medications were stopped 48 h before cardiac catheterization.

Catheterization procedure. With use of 1% lidocaine for local anesthesia, left and right heart catheterization was performed percutaneously. A 7F high fidelity double-tipped micromanometer catheter (PC 770, Millar Instruments) was passed into the left ventricle through a femoral artery and positioned to record left ventricular and aortic pressure simultaneously. An 8F pigtail angiographic catheter (Cordis Laboratory) was positioned in the left ventricle through the other femoral artery. There was no local vascular complication in any of the studied patients.

After the catheters were positioned and heart rate and blood pressure returned to precatheterization levels, left ventriculography (1 ml/kg ioxaglate) was performed in the 30° right anterior oblique view (100 frames/s) with simultaneous recording of left ventricular and aortic pressures and exposed frame marker (paper speed 100 mm/s).

Data analysis and calculations. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume were calculated using the area-length method (12). Left ventricular wall thickness (hm) was measured at end-diastole at the equator of the left ventricle. Actual wall thickness at end-diastole (h_{ED}) was calculated after correction for X-ray image distortion by filming a calibrated grid at the assumed location of the left ventricle; the ratio of true length on the grid to the measured length corresponding to it on the film was the correction factor (CF). *The actual thickness was obtained by the following equation:*

$$h_{ED}\ (cm) = hm\ (cm) \cdot CF.$$

The value of h_{ED} was used to calculate the left ventricular myocardial wall volume (Vw) according to the equation of Trenouth et al. (13):

$$Vw\ (ml) = (4\pi/3) \cdot [(L_{ED} + h_{ED})/2] \cdot [(D_{ED}/2) + h_{ED}]2 - LVEDV\ (ml),$$

where L_{ED} (cm) is the major axis of the left ventricle at end-diastole (measured major axis on the angiogram corrected by the correction factor) and D_{ED} (cm) is the minor calculated axis of the left ventricle at end-diastole, derived from the left ventricular end-diastolic volume calculated by the area-length method (12):

$$D_{ED} = (\sqrt{6LVEDV/\pi.L_{ED}}).$$

The left ventricular myocardial wall volume was then assumed to be constant, and its value was used to calculate end-systolic wall thickness (h_{ES}).

Left ventricular pressure-volume data were analyzed by hand. End-systolic pressure was determined on the pressure recordings by the frame mark corresponding to the smallest calculated left ventricular volume.

Average left ventricular end-systolic equatorial wall stress (ESS, g/cm²) was calculated using the equation of Falsetti et al. (14) for an ellipsoidal geometry of the left ventricle:

$$ESS = (Pb/h_{ES}) \cdot (2a^2 - b^2)/(2a^2 + bh_{ES}),$$

where P (mm Hg) is the left ventricular pressure corresponding to the smallest left ventricular volume, a (cm) is the measured end-systolic major semi-axis, b (cm) is the calculated end-systolic minor semi-axis and h_{ES} (cm) is the calculated end-systolic wall thickness.

Statistical analysis. The relation between the end-systolic stress/volume ratio and end-diastolic volume was determined within each group by linear regression analysis using the least squares method. The comparison of regression lines between the aortic stenosis and normal groups and aortic regurgitation and cardiomyopathy groups was performed using variance analysis to compare the slopes, and covariance analysis to compare the intercepts (15). The mean end-systolic stress/volume ratio in the four patients with aortic stenosis and a significantly dilated left ventricle (that is, patients with end-diastolic volume >95% upper confidence interval of normal) was compared with the mean end-systolic stress/volume ratio in the four patients with cardiomyopathy and similar end-diastolic volume values. Comparison of means was performed using the *t* test. For all analyses, significance was assigned at $p < 0.05$.

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Table 1. Left Ventricular Volumes and Stress-Related Variables

	EDV (ml)	ESV (ml)	ESS (g/cm^2)	ESSVR (g/cm^2 per ml)
NL	132 ± 25	52 ± 13	220 ± 44	4.35 ± 0.80
(n = 18)	(89–191)	(31–80)	(150–349)	(3.38–5.59)
AS	142 ± 31	59 ± 22	232 ± 82	4.33 ± 1.75
(n = 24)	(96–212)	(22–110)	(93–397)	(1.53–8.04)
AR	361 ± 129	202 ± 101	399 ± 101	2.28 ± 0.81
(n = 18)	(173–678)	(52–420)	(213–618)	(1.19–4.38)
MR	236 ± 38	105 ± 32	274 ± 74	2.71 ± 0.60
(n = 9)	(177–285)	(47–154)	(193–393)	(2.03–4.11)
CM	252 ± 80	174 ± 77	340 ± 87	2.21 ± 0.61
(n = 35)	(120–454)	(69–388)	(209–509)	(0.84–3.28)

Values are mean values ± SD; range is shown in parentheses. AR = aortic regurgitation; AS = aortic stenosis; CM = cardiomyopathy; EDV = end-diastolic volume; ESS = end-systolic stress; ESSVR = end-systolic stress/volume ratio; ESV = end-systolic volume; MR = mitral regurgitation; NL = normal subjects.

Results

Left ventricular volumes and stress-related variables are presented for each group in Table 1. An inverse relation was observed for each group between the end-systolic stress/volume ratio and end-diastolic volume (that is, the larger the left ventricular cavity, the smaller the end-systolic stress/volume ratio) (Fig. 1). An inverse relation to end-diastolic volume was also evidenced when the end-systolic stress/volume ratio was "normalized" to body surface area in normal subjects (Fig. 2), but no relation was found when it was normalized to left ventricular end-diastolic volume (Fig. 2).

Variables in the valvular disease and cardiomyopathy group. Average values for end-systolic stress/volume ratio and end-diastolic volume were similar in patients with a normal left ventricle and in those with aortic stenosis. The slope of the end-systolic stress/volume ratio–end-diastolic volume relation—a marker of the size dependence of the end-systolic stress/volume ratio—was not significantly different in these two groups (Table 2). The slope of the end-systolic stress/volume ratio-end-diastolic volume relation was similar in patients with aortic regurgitation, mitral regurgitation and cardiomyopathy, but the intercepts (Table 2) were significantly different ($p < 0.01$). At a given end-diastolic volume, the mean end-systolic stress/volume ratio was higher in the aortic regurgitation group than in the cardiomyopathy group, as assessed by absence of overlapping of the 95% confidence interval.

Finally, in the aortic stenosis group, the four patients with the greatest left ventricular dilation had an end-systolic stress/volume ratio similar to that of the four patients with cardiomyopathy and comparable left ventricular size (2.39 versus 2.89, respectively, p = NS).

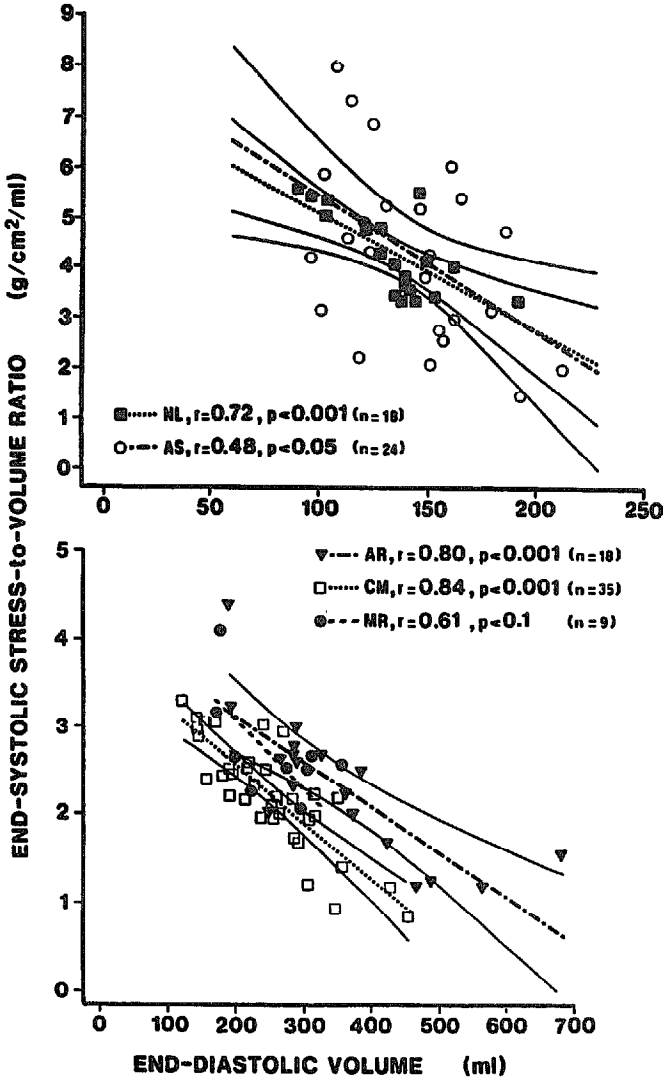

Figure 1. Relations between end-systolic stress/volume ratio and end-diastolic volume. For each group of patients, linear regression values and the 95% confidence interval are represented. AR = aortic regurgitation; AS = aortic stenosis; CM = cardiomyopathy; MR = mitral regurgitation; NL = normal subjects.

Discussion

Comparison of the inotropic state of the ventricle in patients with different diseases by means of the end-systolic stress/volume ratio is affected by the dependence of this index on chamber size. Although this dependence was suggested in previous reports (8–11), it has not been confirmed in a large number of patients. The present study included a large series of patients with a normal ventricle, as well as patients with various types of ventricular hypertrophy or dilation, or both, and therefore provides data that may settle the problem in the clinical assessment of left ventricular function.

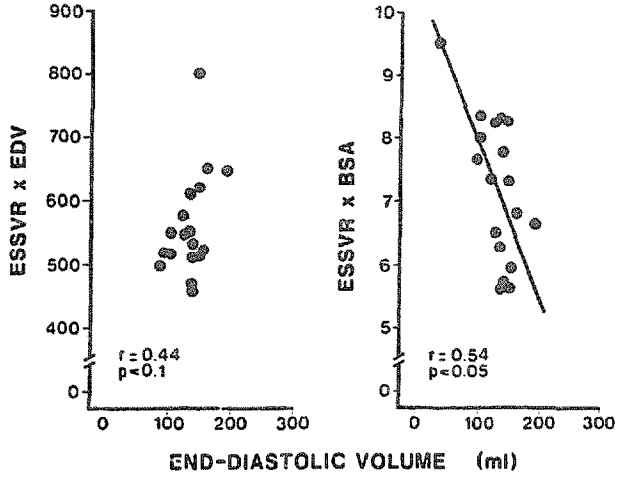

Figure 2. **Left panel,** Attempt at normalization of the end-systolic stress/volume ratio (ESSVR) by end-diastolic volume (EDV) in 18 normal subjects. **Right panel,** Attempt at normalization of the end-systolic stress/volume ratio by body surface area (BSA) in the 18 normal subjects.

End-systolic stress-volume ratio and end-diastolic volume relation. Our results demonstrate a linear inverse relation between the end-systolic stress/volume ratio and left ventricular end-diastolic volume in patients with a normal left ventricle. The range of variation of the end-systolic stress/volume ratio was such that two patients whose value for end-diastolic volume differed by 50% would have a 20% difference in end-systolic stress/volume ratio. This relation probably occurs because, whereas aortic pressure (and therefore wall stress) is relatively constant, a larger ventricle will have a greater end-systolic volume. Thus, the end-systolic stress/volume ratio will be lower in a large ventricle than in a smaller heart, even though contractile performance may be presumed to be the same. These findings agree with previous data (16) showing that the normal ventricle of a child has a greater slope of pressure-volume relation at end-systole than does the normal ventricle of an adult.

Table 2. Values of y Axis Intercept and Slope of the Linear Regression Line of the Relation Between End-Systolic Stress/Volume Ratio and End-Diastolic Volume

	y Axis Intercept (ESSVR)	Slope	r Value
NL (n = 18)	7.41	−0.024	0.721
AS (n = 24)	8.14	−0.027	0.484
AR (n = 18)	4.09	−0.006	0.800
MR (n = 9)	4.98	−0.010	0.609
CM (n = 35)	3.81	−0.007	0.838
	(3.75)*	(−0.006)*	(0.768)*

*Calculated using a spheroid model of the left ventricle. Values are mean values ± SD. Abbreviations as in Table 1.

The size dependence of the slope of the pressure-volume relation at end-systole (E_{max}) and the end-systolic stress/volume ratio has led to several "normalization" or "standardization" attempts. In experimental conditions, Belcher et al. (9) established that E_{max} was a function of body or left ventricular weight, and that standardization by regression adjustment diminished its variance without affecting its response to altered contractile performance. Carabello and Spann (4) also stated that indexing left ventricular volume by body size tended to decrease the dispersion of E_{max}. In humans, previous attempts (17–19) to determine an ideal variable that would take into account these normalization problems have been disappointing. Correction by end-diastolic volume or body surface has been proposed as part of a normalization scheme. Yet, neither in previous reports nor in our studies were these attempts successful, and normalized indexes were still dependent on ventricular size (Fig. 2). Thus, as recommended by Mirsky et al. (20), relations rather than simple normalized variables appear to be required for a reliable comparative assessment of the contractile performance in patients with different chamber size.

Aortic stenosis: role of hypertrophy. The end-systolic stress/volume ratio–end-diastolic volume relation enables interpatient comparison of inotropism at a given left ventricular size. In this study, left ventricular end-diastolic volumes were within the same range in patients with a normal ventricle and in those with aortic stenosis (Fig. 1). The relation of end-systolic stress/volume ratio and end-diastolic volume was similar in the two groups. This critical size dependence of the end-systolic stress/volume ratio in patients with aortic stenosis is explained by the fact that hypertrophy is an important feature of pressure-overloaded ventricles. An increased wall thickness allows stress to remain normal—or low—for a prolonged period of time, during which left ventricular size may progressively increase. Therefore, in the presence of significant wall hypertrophy, even a slight enlargement of the left ventricular dimension will produce a marked reduction of the end-systolic stress/volume ratio, making this index highly dependent on left ventricular size in patients with aortic stenosis.

Volume load: valvular regurgitation and cardiomyopathy. Left ventricular dimensions were also within a comparable range in patients with volume overload due to aortic regurgitation, mitral regurgitation and cardiomyopathy. The slope of the end-systolic stress/volume ratio–end-diastolic volume relation was comparable among the three groups. Yet, at a given end-diastolic volume, end-systolic stress/volume ratio was significantly higher in patients with aortic regurgitation than in those with cardiomyopathy. Thus, for a comparable

degree of ventricular enlargement, the contractile performance of the left ventricle would be better in patients with aortic regurgitation than in those with cardiomyopathy. However, the left ventricular equatorial wall stress calculation could have been altered using an ellipsoid model for a spheroid left ventricular geometry in patients with cardiomyopathy. In our study, it must be pointed out that end-diastolic and end-systolic diameters were derived from left ventricular volume and the actual length of the cavity, so that the calculated diameters were not underestimated in a way that resulted in large differences in equatorial wall stress. Moreover, the relation between the end-systolic stress/volume ratio and end-diastolic volume in patients with cardiomyopathy was calculated using the two models, and the results were not significantly different (Table 2).

An exact delineation of patients with mitral regurgitation is difficult to extrapolate from our results in view of the small number of patients in this group. The end-systolic stress/volume ratio in patients with mitral regurgitation appeared to lie between that in the aortic regurgitation group and the cardiomyopathy group. This suggests that for a similar end-diastolic volume, contractile performance is higher in patients with aortic than in those with mitral regurgitation, and higher in patients with mitral regurgitation than in those with cardiomyopathy. These results agree with the findings of Wisenbaugh et al. (21), which indicate that depressed contractility tends to be more severe in mitral than in aortic regurgitation.

Pressure versus volume overload. As is usually the case, our patients with volume overload had a larger ventricular cavity at the time of cardiac catheterization than did patients with aortic stenosis, thereby prohibiting a direct comparison between these groups. A comparative analysis could, however, be obtained in a subset of patients with aortic stenosis and cardiomyopathy with comparable left ventricular size. For a similar degree of ventricular dilation, the end-systolic stress/volume ratio was comparable in patients with aortic stenosis and cardiomyopathy, suggesting a similar degree of altered contractile performance. This notion, however, has to be cautiously proposed in view of the small number of patients involved in such a comparison. Assessment of ventricular contractile performance in patients with pressure versus volume overload is as yet an unresolved issue, and previous attempts (22–24) to confront these two entities have yielded conflicting results. Our data indicate that at comparable end-diastolic volumes, patients with aortic stenosis and cardiomyopathy have a similar end-systolic stress/volume ratio, but this only concerns a particular range of left ventricular size (specifically, in patients with "advanced" aortic stenosis and those with "early stage" cardiomyopathy). No data were available for patients with cardiomyopathy and normal ventricular size or for patients with aortic stenosis and an extremely dilated ventricle. Thus, the finding of similar contractile performance at a given chamber size in aortic stenosis and cardiomyopathy has to be restricted to patients with "advanced" pressure overload and those with mildly dilated cardiomyopathy.

Conclusions. These data emphasize the size dependence of the end-systolic stress/volume ratio and its consequences for a comparative assessment of patients with pressure and volume overload. An ideal index of myocardial contractile performance would display little sensitivity on the loading conditions of the heart, but also little dependence on the size of the ventricle. Ultimately, it is the balance between these two factors that determines the usefulness of any index dedicated to clinical use. Until such an index is available, attempts to characterize left ventricular contractile performance in patients with pressure or volume overload by means of the end-systolic stress/volume ratio should take into account the size of the left ventricle.

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